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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,190	GRIMPE ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,10-18,21-31 and 34-55* is/are pending in the application.

4a) Of the above claim(s) *4, 7, 10-11, 14-16, 21-22, 35, 37-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12,13,17,18,23-31,34,36 and 55* is/are rejected.

7)☒ Claim(s) *18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of claim amendments, applicant's remarks, and request for RCE, filed 26 September 2007.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 September 2007 has been entered.

Claim Status

Claims 1-4, 7, 10-18, 21-31, 34-55 are pending. Claims 1-3, 12-13, 17-18, 23-24, 26-31, 34 and 36 are amended. Claims 5-6, 8-9, 19-20, and 32-33 are cancelled. Claim 55 is newly submitted. Claims 4, 7, 10-11, 14-16, 21-22, 35, 37-54 were withdrawn by the examiner in the previous Office Action, as being drawn to non-elected inventions. Claims 1-3, 12-13, 17-18, 23-31, 34, 36 and 55 are under current examination.

Priority

This application claims benefit from provisional U.S. Application No. 60/423,082 filed 1 November 2002 and claims benefit from provisional U.S. Application No. 60/471,447 filed 16 May 2003. The instant application has been granted the benefit date, 1 November 2002 from the application 60/423,082.

Response to Arguments - Claim Objections

Applicant's arguments, see page 19 and Claim amendments, filed 26 September 2007, with respect to claim 1 has been fully considered and is persuasive. The claim amendments clearly specify the meaning of "GAG".

Therefore, the objection to claim 1 is hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments, see pages 12-13 and Claim amendments, filed 26 September 2007, with respect to claims 1-3, 12-13, 17-18, 23-24, 26-31, 34 and 36 have been fully considered and are persuasive. The claim amendments clearly incorporate method steps into the amended claims.

. Claims 5-6, 8-9, 19-20, and 32-33 are cancelled and therefore rejection of these claims is moot.

Therefore, the rejections of claims 1-3, 12-13, 17-18, 23-31, 34 and 36 under 35 USC 112, second paragraph are hereby withdrawn.

Response to Arguments – ENABLEMENT (35 USC 112, first paragraph)

Applicant's arguments (pages 13-) and amendments filed 26 September 2007have been fully considered but they are only partially persuasive.

As a consequence of the claim amendments and applicant's arguments the examiner feels impelled to modify the rejection of claims 1-3, 12-13, 17-18, 23-31, 34 and 36 under 35 USC 112, 1st paragraph (scope of enablement).

The examiner accepts the applicant's arguments in light of the Gimpe et al. reference (J Neurosciences. Feb 2004. 24(6): 1393-1397). Although this reference is post-filing art, it is nevertheless, an exact replication of a species of the claimed method and includes additional analysis of the results of the method. These arguments and the Gimpe et al. reference have convinced the examiner that the method of the instant application is enabled for an *in vivo* method of reducing GAG content in a glial scar in a mammal comprising administering to the glial scar of the mammal a DNA enzyme directed to XT-1. The examiner notes that the Gimpe et al. reference was successful in using the XT-1 DNA enzyme by administration using intrathecal administration. The applicants supplement their arguments that intrathecal administration of antisense oligonucleotides has been enabled to reduce expression of genes in nerve cells by providing an additional reference, Lai et al. (Pain 95 (2002): 143-152). The examiner

accepts the applicant's viewpoint that intrathecal administration of various therapeutic nucleic acids (e.g. – antisense oligonucleotides, DNA enzymes, ribozymes, and RNAi constructs) is fully enabled. Therefore, the examiner withdraws the portion of the scope of enablement rejection based on a lack of enablement for *in vivo* methods. In addition to the comments above, the examiner notes that the Gimpe et al. Journal of Neurosciences article was received by the publisher on 6 November 2003, just a few days after the filing date of the instant application, 31 October 2003, further lending credence to the enablement of the claimed methods.

However, the applicant have not addressed the other portion of the examiner's rejection directed to lack of enablement for methods of administration other than topical and intrathecal administration. Since the supporting references also use intrathecal administration, and the claims have not been amended to this scope, the examiner believes, for the reasons of record, that there is not support in the specification for other methods of delivery. Therefore, the examiner maintains the rejection of claims 1-3, 12-13, 17-18, 23-31, 34 and 36 under 35 USC 112, 1st paragraph (scope of enablement), but has narrowed the rejection to cover only the delivery method.

NEW GROUNDS OF REJECTION

Claim Objections

Claim 18 is objected to because of the following informalities: The claim includes a grammatical error; "comprising" should properly be "comprises". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 recites, "The method of claim 29, the agent promoting neurite extension...." The examiner is unsure how this claim further limits claim 29. Is this "promoting neurite extension" a property/characteristic of the agent or a further requirement of the method? If it is a further requirement of the method, what active step is being practiced? The examiner chose not to object to this claim as "not further limiting" and chose to reject it under 112, 2nd paragraph because it seems to lack an active step.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 12-13, 17-18, 23-28, 36 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement;* (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 1 and 17 are broadly drawn, such that they apply to a genus of agents selected from the group consisting of antisense oligonucleotides that bind a nucleic acid sequence encoding proteoglycans, ribozymes, DNA enzymes, RNAi constructs, and small molecules. Furthermore, claim 18 is broadly drawn, such that it encompasses a

large genus of xylotransferases. However, the working examples provided in the instant application only demonstrate individual species of agents, specifically DNA enzymes specific to xylotransferase 1 (XT-1).

While the specification supports the broad definition of agents as encompassing antisense oligonucleotides, ribozymes, DNA enzymes, RNAi constructs, and small molecules, the only demonstration of the claimed in vivo methods utilized specific DNA enzymes directed to XT-1. The specification sufficiently describes a genus of DNA enzymes directed to XT-1 which permit practice of the claimed methods. The specification describes several examples of antisense oligonucleotides which recognize both XT-1 and XT-2, specifically SEQ ID NO:37-38 (page 6) and indicate the sequences to which antisense could be designed, specifically, SEQ ID NO: 1, 3, 5, 7, example 2 (page 94). In particular, Table 1 (pages 100-102) describe a large number of antisense oligonucleotides which could be used. It would not be difficult for an artisan to design antisense oligonucleotides and because of the correlation between the in vitro antisense methods (example 3, page 94) and the enabled DNA enzyme in vitro and in vivo methods, the examiner believes that antisense molecules directed against XT-1 and XT-2 are sufficiently described. Similarly, the specification suggests that specific ribozymes can be targeted to SEQ ID NO:1, 5, and 9. Also, the specification provides a large number of target site for RNAi molecules, specifically, SEQ ID NO:41-102. All of these molecules are specifically directed to inhibiting XT-1.

Despite all this disclosure, the breadth of the claims is still broader than the specification. If the examiner correctly parses the last 3 lines of claims 1 and 17, he

understands that only the antisense oligonucleotides are limited to binding proteoglycans. The ribozymes, DNA enzymes, RNAi constructs, and small molecules need not be targeted to proteoglycans, or more specifically XT-1. Because of the breadth remaining to the agents encompassing the ribozymes, DNA enzymes, RNAi constructs, and small molecules, the examiner asserts that the specification does not support the claimed genus. According to the claims, as amended, these classes of agents must reduce glycosaminoglycan (GAG) content in a glial scar of a mammal when administered, but they need not be directed to targeting proteoglycans. While the emphasis of the specification is directed to inhibiting GAG formation in neuronal scars by inhibiting proteoglycans, the ability of a ribozyme to inhibit expression of some other upstream gene while not directly targeting XT-1, for example, remains within the scope of the amended claim. The specification does not support this breadth of claim language. See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, ***even when accompanied by a method of obtaining the claimed sequence."*** The examiner recommends amending the last lines of claims 1 and 17, so that ribozymes, DNA enzymes, RNAi constructs are also included with the antisense oligos as targeting specific nucleotide sequences encoding xylotransferases I and II (XT-1 and XT-2).

Regarding the claim language encompassing small molecule agents, the examiner does not find sufficient support in the specification to show that a skilled

artisan would recognize that the applicant was in possession of the claimed invention this genus. While the specification states that "one of skill in the art can design small molecules that can occupy that binding pocket (page 44, lines 5-6), this is not a trivial matter and large pharmaceutical companies devote many man-years and much money trying to do just this activity. The examiner does not find this limited direction in the specification sufficient description to support the method comprising administering a genus of agents encompassed by small molecules.

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page

1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the potentially large numbers of agents encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 34 and 36 are rejected under 35 U.S.C. 103(a) as being obvious over Vale et al. (US2001/0049360, published Dec.6, 2001).

Claim 29 is directed to a method for identifying and/or characterizing an agent, the method comprising screening a library of agents capable of one or more of the following: (1) inhibiting the expression of a primary proteoglycans; (ii) inhibiting the expression and/or activity of a chain initiation enzyme; (iii) inhibiting the expression and/or activity of a chain elongation enzyme; or (iv) inhibiting the expression and/or activity of a chain sulfation enzyme. Vale et al. teach, screening a library of probes (page 4, parag.0041) capable of inhibiting expression of betaglycan in cells by antisense inhibition (page 2, parag.0018).

Vale et al. does not teach a pharmaceutical preparation of the agent.

However, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a pharmaceutical preparation of an active ingredient.

The person of ordinary skill in the art would have been motivated to make a pharmaceutical preparation of the agent, because this is common, if not required for use as a therapy.

An artisan would have expected success, because making pharmaceutical preparations have been performed for an extremely long time. Preparations of antisense molecules have also been made in recent years.

Therefore the agent as taught by Vale et al. would have been *prima facie* obvious over the pharmaceutical preparation of the instant application.

Vale et al. teach methods of packaging, marketing, and selling the pharmaceutical preparation.

However, it would have been obvious to the person of ordinary skill in the art at the time of the instant invention to apply these business practices to a pharmaceutical preparation of an active ingredient (agent).

The person of ordinary skill in the art would have been motivated to apply these business practices to pharmaceutical preparation of the agent, because this is common, even necessary in the standard practices of the pharmaceutical industry.

An artisan would have expected success, because applying these business practices have been performed in the pharmaceutical industry for a long time.

Therefore the method as taught by Vale et al. would have been *prima facie* obvious over the method of the instant application.

Claims 29-31, 34 and 36 are rejected under 35 U.S.C. 103(a) as being obvious over Hodgson et al. (WO00/73509, IDS 2/14/2005) in view of Taylor et al. (DDT. 1999. vol.4, No.12: 562-567).

Claim 29 is directed to a method for identifying and/or characterizing an agent, the method comprising screening a library of agents capable of one or more of the following: (1) inhibiting the expression of a primary proteoglycans; (ii) inhibiting the expression and/or activity of a chain initiation enzyme; (iii) inhibiting the expression and/or activity of a chain elongation enzyme; or (iv) inhibiting the expression and/or activity of a chain sulfation enzyme. Hodgson et al. teach methods of screening libraries of compounds (abstract). Hodgson et al. teach "human molecules for diagnostics and therapeutics", including "heparin-sulfate 6-sulfotransferase" (Table 1), an enzyme involved in sulfation. Hodgson et al. also teach methods comprising antisense oligonucleotides (page 139-140). Hodgson et al. also teach proteins that are found in glial cells that surround neurons and astrocytes (bottom of page 87 to top of page 88), which could be detected in the methods of Hodgson; the examiner interprets this broadly to mean that genes identified by the methods of Hodgson could satisfy the limitation of claims 30-31. Taylor et al. teach, high throughput methods for screening antisense oligonucleotides (page 562).

While Hodgson and Taylor do not teach antisense oligoribonucleotides, this is an obvious variant of the genus antisense oligonucleotide.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior

art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (high throughput screening methods for antisense oligonucleotides complimentary to nucleic acids encoding sulfation proteins) are taught by Hodgson or Taylor. It would be therefore predictably obvious to use a combination of these elements in a method of identifying agents capable of inhibiting expression of chain sulfation enzymes.

Neither reference teaches a pharmaceutical preparation of the agent.

However, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a pharmaceutical preparation of an active ingredient.

The person of ordinary skill in the art would have been motivated to make a pharmaceutical preparation of the agent, because this is common, if not required for use as a therapy.

An artisan would have expected success, because making pharmaceutical preparations have been performed for an extremely long time. Preparations of antisense molecules have also been made in recent years.

Therefore the agent as taught by Hodgson et al. in view of Taylor et al. would have been *prima facie* obvious over the pharmaceutical preparation of the instant application.

Neither reference teaches methods of packaging, marketing, and selling the pharmaceutical preparation.

However, it would have been obvious to the person of ordinary skill in the art at the time of the instant invention to apply these business practices to a pharmaceutical preparation of an active ingredient (agent).

The person of ordinary skill in the art would have been motivated to apply these business practices to pharmaceutical preparation of the agent, because this is common, even necessary in the standard practices of the pharmaceutical industry.

An artisan would have expected success, because applying these business practices have been performed in the pharmaceutical industry for a long time.

Therefore the method as taught by Hodgson et al. in view of Taylor et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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